UNIVERSITY OF OKLAHOMA MEDICAL CENTER

ABSENCE OF A DIRECT TOXIC ACTION OF ENDOTOXIN ON MYOCARDIAL TISSUE

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Technical Report No. 36
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MEDICAL CENTER RESEARCH AND DEVELOPMENT OFFICE
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800 Northeast Thirteenth Street
Oklahoma City, Oklahoma 73104

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January 22, 1970

Research sponsored by the Office of Naval Research
Contract N00014-68-A-0496
Project NR 105-516

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The question of the precise role of the heart in endotoxin shock has been largely unresolved. Although it is generally agreed that the heart may ultimately fail, its possible contributory role in the initial development of this irreversible state is one of serious question. Experiments carried out on both the canine and primate species demonstrate that venous return markedly decreases early after endotoxin[1-4] due to intravascular pooling. It appears therefore that systemic hypotension is in large part precipitated by peripheral rather than direct cardiac mechanisms.

Weil and others found no evidence for myocardial failure in the early phase of canine endotoxin shock: cardiac arrhythmias did not occur and conduction defects were not observed.[1] Londe and others found that large doses of endotoxin produced no perceptible effect on the myocardial extraction of oxygen and that the coronary vasculature was unaffected.[5] Others have suggested that the heart is only affected indirectly by endotoxin because of unfavorable circulatory conditions.[6] On the other hand, Solis and Downing[7] and others[8] both demonstrated cardiac depression early after endotoxin. In each instance, ventricular contractile force was diminished, and, in the former instance[7], contractile force was depressed even when arterial pressure was maintained.

The purpose of the following study was to determine if the heart is directly damaged by lethal injections of endotoxin under conditions in which respiratory and hemodynamic parameters are maintained constant. The aim of the investigation was to gain an insight into the role of the heart in contributing to the development of irreversible shock.

METHODS

Experiments were conducted on adult mongrel dogs intravenously anesthetized with sodium pentobarbital, 30 mg/kg. The basic procedure was to support an isolated denervated left ventricle by blood exchanged with a heparinized support animal (average weight, 21 kg). Details of the procedure are as follows: The donor heart dog (average weight, 8.4 kg) was anesthetized, and the chest opened along the midsternum region after the animal was placed on a constant volume respirator. The azygous vein and subclavian artery were ligated and sectioned between ties. Ligatures were loosely placed around the thoracic aorta distal to the subclavian artery, the brachiocephalic artery, and superior and inferior vena cavae. The pericardial sac was opened along its ventral surface and the animal was heparinized (3-5 mg/kg). The vagi were then cut in the neck region and the brachiocephalic artery was cannulated with a plastic tubing elevated to a height of 100-125 cm above the heart level. The superior vena cava was cannulated with a blood filled plastic tubing led through a roller-type blood pump drawing blood from the inferior vena cava of the support dog. The tip of this tubing lay in the central vein of the animal proximal to the hepatic vein orifice. To prepare the donor heart for transfer to the perfusion system without interruption of blood flow, the brachiocephalic outflow from the heart was opened, allowing blood to fill the tubing exerting a hydrostatic pressure providing adequate coronary perfusion (pressure > 80 mmHg). The aorta was then tied distal to the brachiocephalic artery, the superior vena caval inflow from the pump was commenced at 120 cc/minute, and the inferior vena cava was immediately ligated. Blood from the aortic outflow was collected in a plastic reservoir and returned to the dog perfusing the heart

at a flow rate equal to the superior vena caval inflow. The heart and lungs were then removed from the chest and transferred to the external system with adequate coronary pressure and flow constantly provided.

A strain gauge arch was sutured to the lateral wall of the left ventricle for measurement of myocardial contractile force. The left ventricular pressure was measured by insertion of a short large bore plastic cannula through the apex of the ventricle with the tip resting within its chamber.

The next procedure was to bypass the right heart which was accomplished after first placing a saline filled plastic drainage tubing into the right ventricle via the atrium and cannulating the pulmonary artery from a T connection previously secured to the superior vena caval inflow tubing. The cannulation of the pulmonary artery required only a few seconds during which time the coronary vessels were retrograde-perfused with blood by hydrostatic pressure from the aortic outflow tubing. Coronary venous blood was collected from the right ventricular drainage tubing into a plastic reservoir and together with brachiocephalic outflow returned to the dog via a second pump (Figure 1). Cardiac output was taken as the sum of aortic outflow and coronary flow, both measured with a cylinder and stop watch. Temperature of coronary venous blood was monitored with a temperature probe. Aortic pressure, left ventricular pressure, cardiac contractility of the isolated heart, and the mean systemic pressure of the support dog, were continuously monitored on a Sanborn recorder. Left ventricular pressure was alternately recorded by means of a Statham pressure transducer, on a sensitive (0-40 mmHg) range and a scale (0-200) registering both systolic and diastolic pressures.

Mean aortic pressure and cardiac output were steadily increased in the isolated heart preparation by adjustment of a screw clamp on the aortic

outflow and elevation of pump speed supplying the pulmonary artery. The lungs of the isolated heart preparation were continuously ventilated by a Starling constant volume respirator. Coronary arterial and venous pO_2, pCO_2, and pH were followed by utilizing an Instrumentation Laboratories blood gas analyzer. Oxygen content of coronary arterial and venous blood was measured by a Natelson Microgasometer. Simultaneously obtained coronary flow measurements permitted the calculation of oxygen uptake by multiplying the A-V O_2 difference by coronary flow.

During an equilibration period, aortic pressures were stabilized at approximately 125-130 mmHg and cardiac output at 50 cc/min/kg body weight based on the weight of the heart donor dog. These pressure and flow values supported and maintained left ventricular systolic and diastolic pressures, coronary flow, coronary blood temperature and oxygen uptake in the physiological range and were therefore maintained constant during the course of the experiments (180 minutes). Following the equilibration period, when all values of the various parameters achieved a relative constancy, a thirty minute control period was run and completed by the injection of an LD_{90} *E. coli* endotoxin (Difco, Detroit), 1.5 mg/kg. Endotoxin was administered intravenously in the support animal and in some experiments additionally injected into the pulmonary arterial inflow of the isolated heart. Experiments were concluded at the death of the dogs or not later than 180 minutes post-endotoxin.

Stroke work[10] in gram·meters was calculated from the formula:

$$\frac{(MAP-LVEDP)\ (SV)\ (1.36)}{100}$$

where MAP = mean aortic pressure (mmHg); LVEDP = left ventricular end diastolic pressure (mmHg) and SV = stroke volume in ml, determined by

dividing cardiac output by heart rate. The acceleration component of ventricular stroke work was disregarded in the calculations on the basis that it represents less than 1 per cent of total stroke work.[11] Cardiac power was determined by the expression of work per second.

The maximum change in pressure per second (dP/dT)[10,12] occurring during isometric contraction of the left ventricle was determined from analysis of the slope of a line drawn tangentially to the steepest portion of the ventricular tracing and expressed in mmHg/sec.

RESULTS

Table I illustrates the effect of an LD_{90} intravenous injection of endotoxin in the intact support dogs supplying blood to the isolated heart. Mean systemic pressure falls markedly and remains low during the post-endotoxin period while heart rate is insignificantly altered.

Several parameters were maintained constant in the perfused heart-lung preparation and these are shown in Table II. Mean aortic pressure, cardiac output, blood temperature and respiration rate and depth were all maintained relatively constant in each experiment. It is noted that although systemic pressure of the support dog fell to severely low values after endotoxin injection, aortic pressure of the heart was maintained in the normal range. These values were deliberately maintained constant because of their direct influences on various work performance and metabolic characteristics of the heart.[13,14]

Table III demonstrates the effect of endotoxin on the hemodynamics and metabolism of the isolated heart. Every individual heart preparation showed marked coronary hemodynamic alterations, coronary flow increasing, and coronary vascular resistance decreasing, in all experiments. Mean coronary flow increased nearly sixty per cent above control while resistance fell to approximately half the initial values, within two hours after endotoxin administration. Data in Table III show that oxygen uptake of the left ventricle varies insignificantly during the control and shock stages. Oxygen uptake was assumed to be negligible in atria and right ventricle (bypassed) as was also done by Sarnoff et al., in a similar preparation.[13] There are no regular changes in heart rate although no experiment demonstrated bradycardia after endotoxin.

It was decided to evaluate the effects of endotoxin on certain cardiac performance parameters and Table IV describes the average results. Left ventricular contractile force does not decrease in any experiment but ordinarily increases; however, because of individual variation, mean values are statistically unaltered by endotoxin. Left ventricular end diastolic pressure (LVEDP) usually decreases in individual hearts following endotoxin injection and on the average, all values tend to decrease from about 3 mmHg to zero mmHg 2-3 hours after endotoxin. The maximum rate of change in pressure per unit time (dP/dT) during isometric contraction shows a constant average increase during the post-endotoxin period. Stroke work (gram-meters) is relatively unaffected by endotoxin although there is a tendency for a decrease, presumably on the basis of a slight elevation of heart rate in individual experiments. On the other hand, when cardiac work is expressed per unit time (second), i.e., power, there is a high degree of constancy in all values both during the control and shock periods, approximately 12 gram-meters/sec.

Figure 2 is an individual record demonstrating the absence of effect of endotoxin on cardiac performance. Both aortic pressure and cardiac output of the isolated heart were maintained constant for 150 minutes, and although marked and sustained hypotension accompanied by acidosis is clearly observable in the support dog, left ventricular pressure and contractility are unchanged during the total course of the experiment.

The last table summarizes pH, pO_2 and pCO_2 alterations in coronary arterial and venous blood. There is a significant decrease in pH by 30-90 minutes after endotoxin ($p \leq 0.05$), pCO_2 values remain relatively constant, and although pO_2 tends to fall in coronary artery blood and rise in coronary venous blood, because of individual variations, these changes are statistically insignificant.

DISCUSSION

The overall objective of this study was to determine the role of the heart in contributing to the precipitation of irreversible endotoxin shock. Experiments were principally designed to determine if the heart is directly damaged by endotoxin when hemodynamic and respiratory parameters are controlled. To better reveal possible direct toxic actions of endotoxin on the myocardium, aortic pressure, cardiac output, blood temperature and respiratory rate and depth were maintained constant during a 2-3 hour post-endotoxin observation period. Blood was continuously exchanged between an endotoxin-shocked animal and the isolated working heart-lung preparation.

Results fail to reveal a single instance of endotoxin toxicity on myocardial work performance or oxidative metabolism studied under the conditions of these experiments. Coronary flow markedly increased and coronary vascular resistance decreased, while myocardial oxygen uptake remained relatively unchanged during the shock period. Left ventricular contractile force and dP/dT increased in all individual experiments after endotoxin administration, while stroke work and particularly cardiac power, remained relatively constant during the three hour shock period. Left ventricular end diastolic pressure did not increase in a single experiment after endotoxin injection, but ordinarily demonstrated a steady decrease. The presence of severe systemic hypotension and acidosis in the animal exchanging blood with the isolated working heart failed to elicit detrimental responses of the heart. Results from the present study therefore offer no support for a direct toxic action of endotoxin on myocardial tissue. These findings support the conclusions of some investigators[1,5,6] but are in disagreement with others[7,8]. It should be noted that the precise role of the heart in hemorrhagic shock is also in serious question because of

contradictory findings. Albert and others[15] ascribed primary heart failure as the initiating deleterious factor in hemorrhage experiments. On the other hand, others[16] reported that the heart is damaged only subsequently to prolonged hemorrhagic hypotension. It has also been reported that cardiac function is only temporarily depressed in hemorrhagic shock and ultimately recovers during the hypotensive state.[17]

Lefer and others[18,19] have identified a myocardial depressor substance present in the plasma of animals in late hemorrhagic shock. They have postulated that this substance may play an important role in the pathogenesis of irreversibility by depressing excitation-contraction coupling or by impairing the cardiac contractile machinery directly. The present study, however, provides no evidence for the release of a myocardial depressant factor in the plasma of the endotoxin-poisoned animal. It is conceivable, however, that an inotropic adrenergic endogenous agent release subsequent to hypotension after endotoxin, could have masked the myocardial effects of a circulating myocardial depressant substance.

The problem of the precise role of the heart in the development of irreversible endotoxin shock is complicated by events occurring in the periphery which most assuredly adversely influence cardiac output[1,4] causing its decrease on the basis of a diminished venous return, and the resultant systemic hypotension may ultimately compromise cardiac integrity because of diminished coronary blood flow. Another major question remains, however, and it is concerned with the possibility of direct myocardial endotoxin toxicity. Gilbert[20] in an earlier review comments that there is no evidence for a direct adverse effect of endotoxin on myocardial function. More recently, others[21,22] have demonstrated myocardial failure in septic shock

in patients, and a logical argument for a general "cardiac theory" of shock has been developed.[23,24] Results from the present study strongly suggest that primary cardiac endotoxin-induced toxicity is not a significant factor in the pathogenesis of experimental septic shock but does not exclude the possibility that indirect effects of endotoxin may perform important roles in the eventual depression of cardiac integrity.

SUMMARY

The effect of endotoxin on the heart is obscure and results have been controversial. The purpose of the present study was to determine if there was a direct detrimental action of endotoxin on cardiac tissue. An isolated heart and ventilated lungs removed from a donor dog were perfused with venous blood from an intact heparinized animal. Pulmonary blood flow, aortic pressure, respiration, and blood temperature were maintained constant in the isolated preparation. Cardiac output was directly measured from aortic and coronary venous outflows. Left ventricular myocardial contractile force, intraventricular and aortic pressure and oxygen uptake were determined. An LD_{90} injection of E. coli endotoxin was intravenously administered to the dog. Results indicate that endotoxin has no detrimental effect on the isolated heart under the conditions of these experiments. Oxygen uptake and left ventricular contractile force were maintained at pre-endotoxin values or increased above control in the presence of severe systemic hypotension in the dog. Left ventricular end diastolic pressure was not elevated in any experiment but ordinarily decreased after endotoxin. Coronary blood flow progressively increased and vascular resistance significantly fell. No regular relationship between heart rate and coronary resistance was observed. In conclusion, there was no evidence to support a direct toxic action of endotoxin on myocardial tissue.

*Acknowledgments. Appreciation is expressed to the following persons for their technical assistance: R. T. Brantley, Janet Camp, Hubert Jennings, Susan Owen, Mary Marple, and Joe Cope.

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LEGEND

Figure 1. Diagram of isolated perfused heart preparation. Blood is obtained from central vein of the dog (catheter tip within thorax) and subsequently returned to femoral vein.

PA ---------- pulmonary artery

A ---------- aorta

BC ---------- brachiocephalic artery

RA ---------- right atrium

RV ---------- right ventricle

LV ---------- left ventricle

AZ ---------- azygous vein

SVC ---------- superior vena cava

IVC ---------- inferior vena cava

SC ---------- adjustable screw clamp

resp ---------- constant volume respirator

SGA ---------- strain gauge arch

LVC ---------- left ventricular catheter

CVC ---------- coronary vein catheter

TP ---------- temperature probe

WB ---------- water bath at controlled temperature

Figure 2. Experiment demonstrating absence of deleterious effect of endotoxin on cardiac performance. (Aortic pressure and cardiac output of isolated heart maintained constant during experiment.)

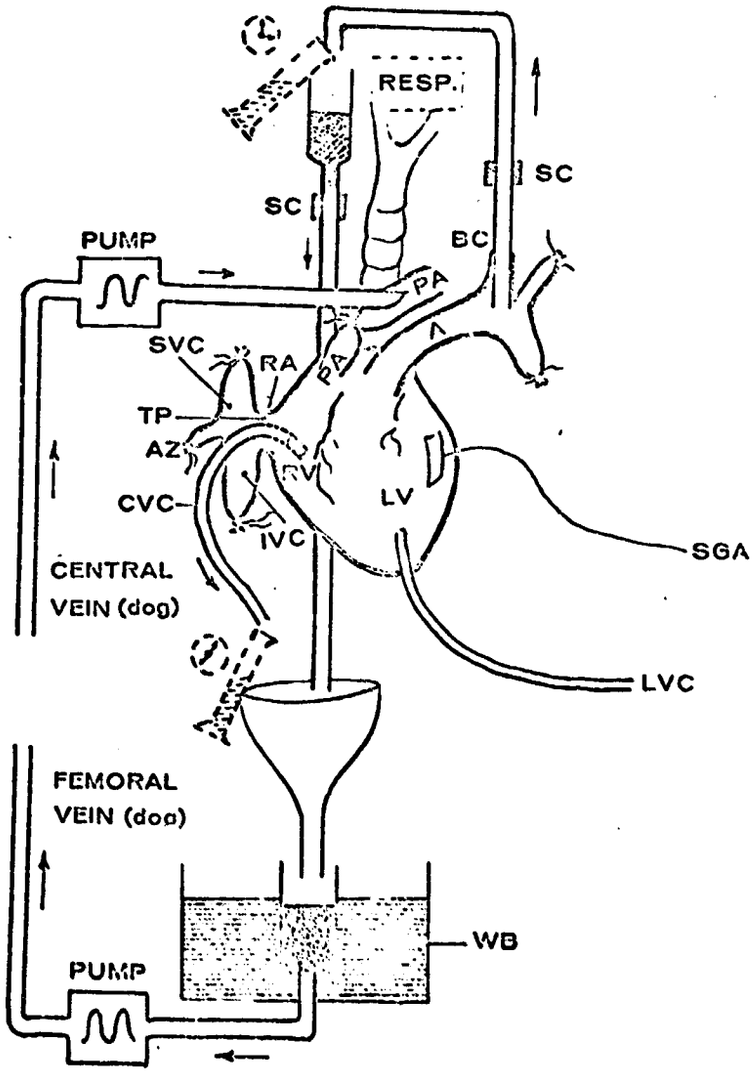

FIGURE 1 - See legend for figures

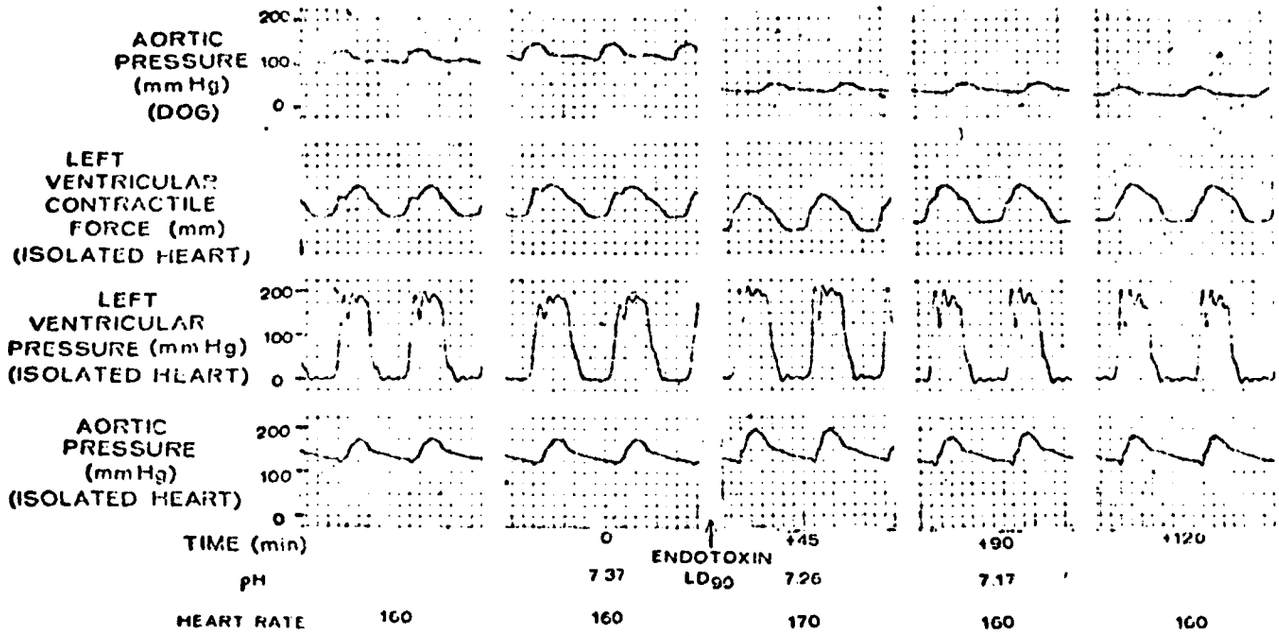

FIGURE 2 - See legend for figures

Table I. Effect of Endotoxin (LD_{90}) on Intact Support Animal (Mean ± SE; N = 7).

Period	Mean Systemic Arterial Pressure (mmHg)	Heart Rate (min.)
Control #1 (Minus 30 min.)	126(± 4)	156(± 7)
Control #2 (Zero time)	127(± 4)	144(± 12)
Post-endotoxin:		
30-90 min.	52(± 9)	155(± 8)
90-150 min.	48(± 6)	162(± 9)
150-180 min.	54(± 11)	173(± 17)

Table II. Controlled Parameters in Isolated Heart Preparation* (Mean ± SE, N = 7).

Period	Mean Aortic Pressure (mmHg)	Cardiac Output cc/min	Cardiac Output cc/min/kg**	Coronary Venous Blood Temperature (°C)
Control #1 (Minus 30 min.)	129(± 8)	405(± 36)	51(± 6)	35.9(± 0.3)
Control #2 (Zero time)	129(± 8)	407(± 37)	51(± 6)	35.9(± 0.4)
Post-endotoxin:				
30-90 min.	126(± 9)	404(± 40)	51(± 6)	35.6(± 0.3)
90-150 min.	121(± 9)	401(± 44)	51(± 7)	35.6(± 0.5)
150-180 min.	126(± 10)	385(± 66)	49(± 9)	36.2(± 0.5)

* Respiration rate and depth maintained constant in each experiment

** Cardiac output value based on weight of dog supplying heart

Table III. Effect of Endotoxin (LD_{90}) on Hemodynamics and Metabolism of Isolated Heart Preparation (Mean ± SE; N = 7).

Period	Coronary Flow (cc/min)	Coronary Vascular Resistance (mmHg/cc/min)	Heart Rate (min)	Oxygen Uptake (cc/min/100gms left ventricle)
Control #1 (Minus 30 min.)	97(± 16)	1.46(± 0.13)	143(± 8)	14.2(± 2.1)
Control #2 (Zero time)	95*(± 19)	1.54(± 0.19)	144(± 11)	11.7**(± 2.0)
Post-endotoxin:				
30-90 min.	142(± 27)	0.96(± 0.13)	163(± 5)	17.1(± 5.9)
90-150 min.	159(± 25)	0.79(± 0.07)	157(± 5)	12.5(± 3)
150-180 min.	160(± 26)	0.74(± 0.04)	151(± 7)	13.5(± 2.3)

* 191(± 43) cc/min/100gms left ventricle
  137(± 30) cc/min/100gms heart

** 8.4(± 1.4) cc/min/100gms heart

Table IV. Effect of Endotoxin on Cardiac Performance (Mean ± SE; N = 7).

Period	Left Ventricular Contractile Force (mm)*	LVEDP** (mmHg)	dP/dT (mmHg/sec)	Stroke Work (gm·meter)	Power (work/sec)
Control #1 (Minus 30 min.)	21.4(± 2.7)	+4.0(± 0.8)	3501(± 617)	5.1(± 0.6)	11.9(± 1.6)
Control #2 (Zero time)	21.8(± 1.9)	+2.7(± 1.2)	2797(± 497)	5.1(± 0.8)	12.0(± 1.6)
Post-endotoxin:					
30-90 min.	26.2(± 4.3)	+0.4(± 0.8)	5012(± 1428)	4.4(± 0.6)	11.8(± 1.7)
90-150 min.	30.4(± 5.7)	-0.2(± 1.1)	4416(± 1192)	4.2(± 0.7)	11.5(± 1.9)
150-180 min.	25.8(± 2.8)	0(± 1.5)	4198(± 831)	4.8(± 0.9)	12.2(± 2.1)

* Measured by strain gauge arch

** LVEDP = Left ventricular end diastolic pressure

Table V. Effect of Endotoxin on pH and Blood Gas Tensions in Isolated Heart Preparation (Mean ± SE; N = 7).

Period		pH*	pO_2	pCO_2
Control #1 (Minus 30 min)	A	7.49(± 0.03)	70(± 8)	22(± 2)
	V	7.46(± 0.03)	24(± 2)	28(± 2)
Control #2 (Zero time)	A	7.50(± 0.04)	73(± 8)	22(± 2)
	V	7.46(± 0.04)	24(± 3)	28(± 3)
Post-endotoxin:				
30-90 min.	A	7.37(± 0.04)	64(± 9)	22(± 2)
	V	7.35(± 0.04)	29(± 3)	27(± 3)
90-150 min.	A	7.31(± 0.06)	55(± 5)	25(± 2)
	V	7.29(± 0.06)	33(± 2)	29(± 2)
150-180 min.	A	7.32(± 0.10)	64(± 8)	24(± 2)
	V	7.31(± 0.10)	36(± 5)	29(± 3)

* A = Coronary artery
V = Coronary vein

Security Classification

DOCUMENT CONTROL DATA - R & D

Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified

1. ORIGINATING ACTIVITY (Corporate author)	2a. REPORT SECURITY CLASSIFICATION
MEDICAL CENTER RESEARCH AND DEVELOPMENT OFFICE OF THE UNIVERSITY OF OKLAHOMA FOUNDATION, INC.	UNCLASSIFIED
	2b. GROUP UNCLASSIFIED

3. REPORT TITLE

Absence of a Direct Toxic Action of Endotoxin on Myocardial Tissue

4. DESCRIPTIVE NOTES (Type of report and, inclusive dates)

Technical Report

5. AUTHOR(S) (First name, middle initial, last name)

L. B. Hinshaw, L. T. Archer, L. J. Greenfield, C. A. Guenter, and J. A. Miller

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
January 22, 1970	22	24

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
N00014-68-A-0496	
b. PROJECT NO. NR 105-516	36
c.	9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)
d.	

10. DISTRIBUTION STATEMENT

This document has been approved for public release and sale; its distribution is unlimited.

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
	Office of Naval Research

13. ABSTRACT

The effect of endotoxin on the heart is obscure and results have been controversial. The purpose of the present study was to determine if there was a direct detrimental action of endotoxin on cardiac tissue. An isolated heart and ventilated lungs removed from a donor dog were perfused with venous blood from an intact heparinized animal. Pulmonary blood flow, aortic pressure, respiration, and blood temperature were maintained constant in the isolated preparation. Cardiac output was directly measured from aortic and coronary venous outflows. Left ventricular myocardial contractile force, intraventricular and aortic pressure and oxygen uptake were determined. An LD_{90} injection of E. coli endotoxin was intravenously administered to the dog. Results indicate that endotoxin has no detrimental effect on the isolated heart under the conditions of these experiments. Oxygen uptake and left ventricular contractile force were maintained at pre-endotoxin values or increased above control in the presence of severe systemic hypotension in the dog. Left ventricular end diastolic pressure was not elevated in any experiment but ordinarily decreased after endotoxin. Coronary blood flow progressively increased and vascular resistance significantly fell. No regular relationship between heart rate and coronary resistance was observed. In conclusion, there was no evidence to support a direct toxic action of endotoxin on myocardial tissue.